

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 September 2001 (13.09.2001)

PCT

(10) International Publication Number
WO 01/66144 A2

- (51) International Patent Classification⁷: **A61K 45/00**
- (21) International Application Number: PCT/US01/07472
- (22) International Filing Date: 8 March 2001 (08.03.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/187,852 8 March 2000 (08.03.2000) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/187,852 (CIP)
Filed on 8 March 2000 (08.03.2000)
- (71) Applicant (for all designated States except US): **RHODE ISLAND HOSPITAL, A LIFESPAN PARTNER** [US/US]; 593 Eddy Street, Providence, RI 02902 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **CALABRESI, Paul** [US/US]; 27 Glen Avenue, Barrington, RI 02806 (US). **DARNOWSKI, James, W.** [US/US]; 20 Devonshire Drive, Barrington, RI 02806 (US).
- (74) Agent: **BEATTIE, Ingrid, A.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION DRUG THERAPY

(57) Abstract: The invention provides antineoplastic composition containing an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase type I enzyme activity.

COMBINATION DRUG THERAPY

BACKGROUND OF THE INVENTION

This invention relates to cancer chemotherapy.

Chemotherapy for cancer is used primarily for the treatment of nonoperable
5 or metastatic tumors or to supplement primary surgical therapy. Traditional
chemotherapeutic approaches to cancer treatment involve administering agents
which are cytotoxic to tumor cells. However, often such agents also affect normal
cells resulting in adverse side effects.

SUMMARY OF THE INVENTION

10 The invention features a combination of therapeutic agents which
significantly inhibits tumor cell growth with low toxicity. Tumor growth and
development in mammals is reduced following administration of a combination
of a topoisomerase I inhibitor and an inhibitor of angiogenesis. Accordingly, the
invention provides an antineoplastic formulation containing a camptothecin
15 compound and a thrombospondin compound. The camptothecin compound is
camptothecin or an analogue thereof, e.g., irinotecan (camptosar, CPT-11, 7-ethyl-
10-[4-(1-piperidino)-1-piperidino]-carbonloxycamptothecin), topotecan, 20-S-
camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT), 7-ethyl-10-
hydroxy-CPT (SN38), 9-AC³ (NSC603071), TTN (NSC 609699), or 9-
20 dimethylaminomethyl-10-hydroxycamptothecin. A thrombospondin compound is
a polypeptide which contains at least one type I properdin repeat sequence and
inhibits formation of blood vessels. For example, the thrombospondin compound
is purified or recombinant thrombospondin-1(TSP1) or thrombospondin-2 (TSP2)
or a biologically active fragment thereof. Preferably, a biologically active
25 fragment contains the amino acid sequence
XXXWXXWXXWXXCXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXCXXXC (SEQ ID NO:1), WSPS (SEQ ID NO:2), KRFK (SEQ ID
NO:3), or CSVTCG (SEQ ID NO:4). For example, a fragment of TSP1 contains

the amino acid sequence

DGGWSHWSPWSSCSVTCGDGVITRIRLCNSPSPQMNGKPCEGEARETKAC
KKDACPI (SEQ ID NO:5), and a fragment of TSP2 contains the amino acid
sequence of

- 5 DGGWSHWSPWSSCSVTCGVGNITRIRLCNSPVPQMGGKNCKGSGRETKA
CQGAPCPI (SEQ ID NO:6).

Also within the invention is method of inhibiting tumor cell growth in a
mammal by administering to the mammal a composition containing an inhibitor of
angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity. The
10 angiogenesis inhibitor is administered before the topoisomerase inhibitor;
alternatively the topoisomerase I inhibitor is administered before the angiogenesis
inhibitor. In some cases, the inhibitors are administered simultaneously. For
example, the method includes the steps of administering to the mammal a
camptothecin compound and a thrombospondin compound. Preferably, the
15 mammal is a human; however, the methods are applicable for veterinary use. For
example, the agents are administered to treat tumors in cats, dogs, cows, pigs, and
the like. The compounds are administered together in a mixture, simultaneously
via the same or different route, or sequentially via the same or different route. The
compositions are delivered systemically or locally, i.e., directly or in close
20 proximity to a tumor mass.

The combination drug formulation and methods of the invention are safer
and more effective than conventional chemotherapeutic approaches, including
known combination approaches. The combination of a camptothecin compound
and a thrombospondin compound inhibited tumor growth in the absence of
25 significant toxicity.

Other features, objects, and advantages of the invention will be apparent
from the description and from the claims.

DETAILED DESCRIPTION

Angiogenesis inhibitors and inhibitors of topoisomerase I such as
30 camptothecin compounds are used to treat tumors in mammals; however, each of
these agents alone is not effective in the treatment of human cancers. The

combined therapeutic regimen results in a synergistic inhibition of tumor cell growth. As is described below, a combination of these agents confers greater neoplastic activity than either of these classes of agents alone.

Inhibition of DNA topoisomerase I enzymes

5 DNA topoisomerase type 1 enzymes function to effect the levels of DNA supercoiling. A biological activity of topoisomerase I is reduction in the level of DNA supercoiling. DNA transformations performed by DNA topoisomerases are accomplished by the cleavage of either a single strand or both strands the nucleic acid. Type 1 topoisomerases can relax supercoiled DNA (except of reverse
10 gyrases), catenate (or decatenate) single-stranded circular DNAs or duplexes providing that at least one of the molecules contains a nick or gap, or interact with single-stranded circles to introduce topological knots.

Enzyme inhibition leads to the stabilization of the covalent-enzyme-DNA complex (cleavable complex). Topoisomerase type I inhibitory activity of
15 camptothecin or derivatives thereof is determined using methods known in the art, e.g., by the cleavable complex *in vitro* assay described in Hsiang, Y. et al., 1985, J. Biol. Chem., 260:14873-14878. An increase in the amount of compound in the presence of a compound compared to the amount in the absence of the compound indicates that the compound has topoisomerase I inhibitory activity. Activity
20 measured by this or similar assays correlates well with *in vivo* anti-tumor activity of topoisomerase inhibitors in animal models of cancer, e.g., camptothecin and its analogs (Hsiang et al., 1989, Cancer Research, 49:4385-4389 (1989) and Jaxel et al., Cancer Research, 49:1465-1469).

Camptothecin compounds

25 Camptothecin is a naturally-occurring compound derived from the Oriental tree *Camptotheca acuminata*. Although it has been shown to have cytotoxic effects, its use clinically is limited due to unpredictable and formidable toxicities. Two water-soluble camptothecin analogs, topotecan and CPT-11, are safer and better tolerated. Additional water soluble camptothecins are known in the art, e.g.,
30 described in U.S. Patent No. 6, 100,273. Other camptothecin derivatives include 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT) and 7-ethyl-10-hydroxy-CPT (SN38). Camptothecin and its derivatives are inhibitors of

DNA topoisomerase and stimulate DNA cleavage. Other topoisomerase I inhibitors include DNA minor groove binders such as Hoechst 33258 and DNA intercalators such as benzophenanthridine alkaloids and indolocarbazole derivatives, as well as drugs which prevent or reverse topoisomerase I-DNA complex formation (e.g., beta-lapachone, diospyrin, topostatin, topostin, flavonoids).

Inhibition of Angiogenesis

Angiogenesis is a process of tissue vascularization that involves the growth of new developing blood vessels into a tissue. This process is also referred to as neovascularization and is mediated by infiltration of endothelial cells and smooth muscle cells. Blood vessels can sprout from pre-existing vessels, de-novo development of vessels can arise from precursor cells (vasculogenesis), or existing small vessels can enlarge in diameter.

Inhibiting angiogenesis at or near a tumor site can restrict tumor growth. Inhibitors of angiogenesis include endothelial cell response inhibitors, including collagenase inhibitors, basement membrane turnover inhibitors, angiostatic steroids, fungal-derived angiogenesis inhibitors, platelet factor 4, thrombospondin, arthritis drugs such as D-penicillamine and gold thiomalate, vitamin D analogs, and alpha-interferon.

Angiogenesis or inhibition thereof is determined by measuring the formation of "microvessels" *in vitro* in collagen gel cultures or *in vivo*. A reduction in the amount of new blood vessel formation in the presence of a compound compared to the level in the absence of the compound indicates that the compound is an inhibitor of angiogenesis. A reduction in the amount of expression of angiogenic factors, e.g., vascular endothelial growth factor (VEGF) or VEGF receptors also indicates that a compound inhibits angiogenesis.

Thrombospondin Compounds

Thrombospondins are polypeptide compounds which are characterized by a type I (properdin) repeat, e.g., SEQ ID NO:1, 5 or 6. Thrombospondin-1 is a 450 kDa extracellular matrix protein that functions to suppresses capillary growth. The antiangiogenic region of TSP1 maps to the type I (properdin) repeats. Naturally-

occurring TSP1 is a trimeric extracellular matrix protein that is held together by two cysteine residues. It is one of a family of five TSP proteins that have been described to date. With the exception of TSP5, members of the thrombospondin family are also characterized as having heparin binding capability. However, a
5 heparin binding domain (e.g., located in the amino terminal portion of a naturally-occurring thrombospondin monomer) need not be present for antiangiogenic activity.

Biologically active fragments, mutants, or analogues of TSP1 or TSP are tested for the ability to inhibit angiogenesis. Fragments are recombinantly
10 produced or generated by enzymatic digestion. Fragments and analogues of human thrombospondin with antiangiogenesis activity are known in the art (e.g., as described in U.S. Patent No. 5,192,744 or U.S. Patent No. 5,840,692). Inhibition of angiogenesis is measured using methods well known in the art, e.g., a standard in vivo corneal neovascularization assay (Polverini et al., 1991, Methods.
15 Enzymol. 198:440-450).

Therapeutic Administration

Camptothecin or thrombospondin compounds are formulated as colloidal dispersions or dissolved in a pharmaceutically-acceptable diluent, e.g., sterile water, physiological saline, or a dextrose solution (e.g., 20% dextrose).
20 Alternatively, a camptothecin compound is administered as a liposomal composition; methods for preparing multilamellar liposome-incorporated camptothecin (LCPT) are known in the art (e.g., as described by Clements et al., 1996, Anticancer Drugs 7:851).

The combination drug therapy is used to treat solid, non-solid, and
25 multiple-drug resistant tumors. The tumor is a carcinoma or sarcoma. Tumors to be treated include leukemia, lymphoma, as well as cancers of the colon, lung, melanoma, ovarian, breast, prostate cancer, pancreatic, CNS, liver, and urinary bladder.

An effective amount of a compound is preferably from about 0.1 mg/kg to
30 about 150 mg/kg. The compounds are administered using methods known in the art. They are administered locally, e.g., at the site of a solid tumor, or systemically, e.g., in the case of diffuse, or disseminated tumors. To treat

accessible solid tumors, either agent or both agents are administered in a slow release implant or pellets surgically introduced into or near the site of a solid tumor. Preferably, the compound is administered orally, topically or parenterally, e.g., subcutaneously, intraperitoneally, intramuscularly, and intravenously. The compounds are administered as an admixture, or in separate formulations either simultaneously, or sequentially.

Thrombospondin-1 and Irinotecan Inhibit Tumor Growth

The antineoplastic activity of TSP plus CPT-11 was evaluated in an art-recognized model for cancer, nude mice bearing xenografts of the human colon tumor cell line HT29. TSP and CPT-11 did not interact *in vitro* to produce enhanced tumor cell cytotoxicity. However, *in vivo*, a synergistic antineoplastic effect was observed after administration of TSP and CPT-11 in combination.

For *in vivo* studies, nude mice were inoculated subcutaneously in the left axillary region with 5×10^6 HT29 cells. When tumors were palpable (approximately 50 mg), mice were divided into groups (n=15-22) and treated as follows: (i) no treatment; (ii) TSP alone (5-40 mg/kg intraperitoneally) (iii) CPT-11 alone (100-300 mg/kg intraperitoneally); or (iv) TSP (20 mg/kg) + CPT-11 (150 mg/kg). TSP was injected daily while CPT-11 was administered on days 0, 7, 14, and 21. Mice were weighed and tumors measured twice weekly. By day 28, TSP alone (10 or 20 mg/kg) significantly ($p < 0.05$) inhibited tumor growth. Treated tumor size/Control tumor size (T/C) equaled 0.64 or 0.57, respectively. Treatment with other doses of TSP was less effective. CPT-11 alone, at all doses, also significantly ($p < 0.001$) inhibited tumor growth with an average T/C of 0.3. However, CPT-11 at 250 mg/kg and 300 mg/kg induced significant toxicity and mortality. When TSP was combined with CPT-11, a highly significant inhibition of tumor growth was observed compared to control (T/C = 0.1, with $p = 0.00002$) and compared to CPT-11 alone ($p = 0.0008$). The inhibition of tumor growth observed with the combination drug therapy was without significant toxicity. These results indicate that combinations of chemotherapeutic agents (e.g., topoisomerase I inhibitors such as camptothecins) and agents which inhibit angiogenesis (e.g., thrombospondins) are useful to inhibit tumor growth while avoiding detrimental side effects such as toxicity.

Other embodiments are within the following claims.

What is claimed is:

/

1. An antineoplastic composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity.
2. The antineoplastic composition of claim 1, wherein said inhibitor of angiogenesis is a thrombospondin compound.
3. The antineoplastic composition of claim 1, wherein said inhibitor of DNA topoisomerase I enzyme activity is a camptothecin compound.
4. The antineoplastic composition of claim 2, wherein said thrombospondin compound is thrombospondin-1.
5. The antineoplastic composition of claim 2, wherein said thrombospondin compound is thrombospondin-2.
6. The antineoplastic composition of claim 3, wherein said camptothecin compound is irinotecan (CPT-11).
7. The antineoplastic composition of claim 3, wherein said camptothecin compound is topotecan.
8. The antineoplastic composition of claim 3, wherein said camptothecin compound is selected from the group consisting of 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT), 7-ethyl-10-hydroxy-CPT (SN38), and 9-AC³.
9. A method of inhibiting tumor cell growth in a mammal, comprising administering to said mammal a composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity.
10. The method of claim 9, wherein said inhibitor of angiogenesis is a thrombospondin compound.

11. The method of claim 9, wherein said inhibitor of DNA topoisomerase I enzyme activity is a camptothecin compound.
12. The method of claim 10, wherein said thrombospondin compound is
5 thrombospondin-1.
13. The method of claim 10, wherein said thrombospondin compound is thrombospondin-2.
- 10 14. The method of claim 11, wherein said camptothecin compound is irinotecan (CPT-11).
15. The method of claim 11, wherein said camptothecin compound is topotecan.
15
16. The method of claim 11, wherein said camptothecin compound is selected from the group consisting of 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT), 7-ethyl-10-hydroxy-CPT (SN38), and 9-AC³.
- 20 17. The method of claim 9, wherein said mammal is a human.
18. The method of claim 9, wherein said inhibitor of angiogenesis is administered prior to said inhibitor of DNA topoisomerase I enzyme activity.
- 25 19. The method of claim 9, wherein said inhibitor of DNA topoisomerase I enzyme activity is administered prior to said inhibitor of angiogenesis .
20. The method of claim 9, wherein said inhibitor of angiogenesis and said inhibitor of DNA topoisomerase I enzyme activity are administered
30 simultaneously.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 September 2001 (13.09.2001)

PCT

(10) International Publication Number
WO 01/66144 A3

- (51) International Patent Classification⁷: **A61K 45/06**
- (21) International Application Number: **PCT/US01/07472**
- (22) International Filing Date: **8 March 2001 (08.03.2001)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
60/187,852 **8 March 2000 (08.03.2000)** **US**
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US **60/187,852 (CIP)**
Filed on **8 March 2000 (08.03.2000)**
- (71) Applicant (for all designated States except US): **RHODE ISLAND HOSPITAL, A LIFESPAN PARTNER** [US/US]; 593 Eddy Street, Providence, RI 02902 (US).
- (72) Inventors; and
- (73) Inventors/Applicants (for US only): **CALABRESI, Paul** [US/US]; 27 Glen Avenue, Barrington, RI 02806 (US). **DARNOWSKI, James, W.** [US/US]; 20 Devonshire Drive, Barrington, RI 02806 (US).
- (74) Agent: **BEATTIE, Ingrid, A.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**
- (84) Designated States (regional): **ARIPO** patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), **Eurasian** patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), **European** patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), **OAPI** patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
- (88) Date of publication of the international search report:
28 March 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **ANTINEOPLASTIC COMBINATION COMPRISING AN INHIBITOR OF ANGIOGENESIS AND AN INHIBITOR OF DNA TOPOISOMERASE I ENZYME ACTIVITY**

(57) Abstract: The invention provides antineoplastic composition containing an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase type I enzyme activity.

WO 01/66144 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/07472

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2000 (2000-03) ALLEGRIINI GIAEOMO ET AL: "The angiogenesis inhibitor thrombospondin-1 plus irinotecan significantly inhibit tumor growth in human colon tumor bearing nude mice." Database accession no. PREV200000275647 XP002180182 abstract & PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 813 XP001019254 91st Annual Meeting of the American Association for Cancer Research.; San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X</p> <p style="text-align: right;">-/--</p>	1-20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special Categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *I* earlier document but published on or after the international filing date
- *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

6 December 2001

Date of mailing of the international search report

13/12/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Engl, B

INTERNATIONAL SEARCH REPORT

Inter. onal Application No
PCT/US 01/07472

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	the whole document ---- WO 93 09782 A (SMITHKLINE BEECHAM CORP) 27 May 1993 (1993-05-27) the whole document	1-20
A	---- WO 92 14470 A (SMITHKLINE BEECHAM CORP) 3 September 1992 (1992-09-03) the whole document	1-20
A	---- WO 91 10424 A (UNIV NORTHWESTERN) 25 July 1991 (1991-07-25) the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 01/07472

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9309782	A	27-05-1993	AU 671605 B2	05-09-1996
			AU 3137993 A	15-06-1993
			CA 2123321 A1	27-05-1993
			EP 0612248 A1	31-08-1994
			JP 7501079 T	02-02-1995
			MX 9206577 A1	01-05-1993
			NZ 245112 A	26-07-1995
			PT 101061 A ,B	30-06-1994
			WO 9309782 A1	27-05-1993
			US 5633016 A	27-05-1997
			ZA 9208771 A	08-09-1993
WO 9214470	A	03-09-1992	AU 664172 B2	09-11-1995
			AU 1540692 A	15-09-1992
			CA 2104449 A1	22-08-1992
			EP 0572563 A1	08-12-1993
			JP 6505487 T	23-06-1994
			MX 9200725 A1	01-09-1992
			PT 100154 A	31-05-1993
			WO 9214470 A1	03-09-1992
WO 9110424	A	25-07-1991	US 5192744 A	09-03-1993
			AT 126065 T	15-08-1995
			CA 2050290 A1	13-07-1991
			DE 69111919 D1	14-09-1995
			DE 69111919 T2	07-12-1995
			DK 463152 T3	06-11-1995
			EP 0463152 A1	02-01-1992
			JP 4504429 T	06-08-1992
			WO 9110424 A1	25-07-1991